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Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/002,485

Applicant(s)

LAL ET AL.

Examiner

Christine J. Saoud

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 20 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,15-18,22-30 and 32-39 is/are pending in the application.
- 4a) Of the above claim(s) 1,15-18,22,23,28 and 34-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-27, 29-30, 32-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of Claims and Application***

The Board of Patent Appeals and Interferences rendered a decision on Appeal No. 2002-0773 in which the rejections of record were affirmed. Additionally, the BPAI included new reasons for affirming the rejections of record, and because the reasons were deemed significant by the BPAI, it was considered a new ground of rejection pursuant to 37 CFR 1.196(b).

Applicant has chosen to submit evidence and argument in response to the new ground of rejection made by the Board pursuant to 37 CFR 1.196(b). Applicant's arguments will be considered by the Examiner in the action that follows.

Applicant states at page 10 of the response in footnote 1 that the claims were subject to an election of species for the nucleic acid molecule which was examined. While Applicant is correct in stating that an election of species was made in the instant application (30 September 1998), the election of species requirement was withdrawn and a new restriction of the claims was made on 16 April 1999. The claims were re-restricted because the original claims contained improper Markush claims and the recited molecules of the claims (proteins and nucleic acids) were indicated to be independent and distinct inventions. Applicant traversed the restriction requirement in the paper dated 14 May 1999 and the Examiner made the restriction final in the paper dated 09 June 2000.

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Claims 1, 15-18, 22-23, 28 and 34-39 are withdrawn pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Additionally, the instant claims include inventions which are withdrawn pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions (see election with traverse in paper dated 14 May 1999). Claims 24-27, 29-30 and 32-33 are under consideration in the instant Office action.

### ***Information Disclosure Statement***

It is noted that Applicant has filed numerous references for consideration in the instant application. It is also noted that Applicant did not file an IDS which includes the references being cited. If a patent were to issue from the instant application, those references cited as evidence would not appear on the face of the patent because they are not included on an IDS or PTO-892.

### ***Claim Rejections - 35 USC §§ 101 and 112***

Claims 24-27, 29-30, and 32-33 stand rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a well-established or a disclosed specific and substantial credible utility. This rejection was set forth in prior Office Action of 09 June 2000 and affirmed by the BPAI on 20 August 2003.

Claims 24-27, 29-30, and 32-33 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101. Specifically, since the claimed invention is not supported by either

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a specific or substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation. This rejection was set forth in prior Office Action of 09 June 2000 and affirmed by the BPAI on 20 August 2003.

***Evidence Cited and Relied Upon by Applicant***

In the response filed 20 October 2003, Applicant has cited 27 different references, press releases, etc. in order to establish the state of the art with regard to microarray technology at the time of the instant invention. Applicant also provides statements regarding the state of the art, presumably based on these references/published documents.

Applicant also has filed 4 Declarations under 37 CFR § 1.132 and 2 CVs of the Declarants. The CVs will not be commented on, as they do not provide evidence to overcome the rejections of record for the claimed invention. Each of the Declarations will be addressed individually, even though Applicant did not specifically address each Declaration in the response.

The Declaration of V. Iyer filed under 37 CFR § 1.132 has been carefully considered, but is not persuasive to overcome the rejections of record. Iyer discusses the use of microarray-based expression profiling in exploring metabolic reprogramming, drug target validation , identification of drug effects, and molecular phenotyping (see page 2 of Declaration). Iyer states that microarrays

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rely on “comparison of patterns of expression” (page 3, top). Iyer cites 4 references (DeRisi et al., Marton et al., Iyer et al. and Ross et al.).

In the DeRisi et al. reference, almost every gene of *S. cerevisiae* was used and expression pattern data did not rely upon any specific gene used in the microarray. Furthermore, when generating expression patterns for drug screening, the comparisons are made looking at the patterns of expression and this information does not require any particular gene or the knowledge of what the genes are (see page 685, columns 1 and 2). DeRisi et al. state at page 685 that

The value of the information from each experiment of this kind will progressively increase as more is learned about the functions of each gene and as additional experiments define the global changes in gene expression in diverse other natural process and genetic perturbations. Perhaps the greatest challenge now is to develop efficient methods for organizing, distributing, interpreting, and extracting insights from the large volumes of data these experiments will provide.

Marton et al. used microarrays to examine secondary drug target effects. The microarrays used by Marton et al. contained more than 6,000 DNA probes from the yeast genome. Data obtained was in the form of a “signature” of expression and conclusions were drawn from differences in the “signature” pattern of expression. Again, the use of the microarray did not require any specific DNA or knowledge of what the DNA encoded.

Iyer et al. measured mRNA levels of 8613 human genes to study gene expression and the response of human fibroblasts to serum. Again, knowledge of what the gene was or did was not required before the gene was placed into

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the microarray. When analyzing the data obtained from the microarray, genes were grouped temporally, and, again, no significance was placed on what the genes encoded or what the genes were.

Ross et al. used approximately 8,000 genes to screen for anti-cancer drugs by looking at the pattern of expression of the genes. Certain types of tissues had distinctive patterns, demonstrating that microarrays can be useful for identifying particular tissue types (i.e. cancerous tissues). The pattern of expression of the genes on the microarray also changes when compounds are administered, and these patterns can be analyzed and compared to known patterns with compounds that have particular biological effects. However, the collection of the genes in the microarray do not appear to be significant or important in order to obtain data to perform these experiments.

The Declaration at paragraph 7 states that arrays with more genes are more useful than microarrays with fewer genes. At paragraph 8 of the Declaration, Iyer concludes that the microarray should include each newly identified gene as a probe. However, the utility of the microarray does not depend on the specific genes/DNA which are included in it; a microarray would be a useful tool to scientists/researchers regardless of what types of genes are included, therefore any DNA/gene should be included on a microarray. Applicant asserts that use of the claimed invention in a microarray is a well-established utility. However, a well-established utility must also be specific, substantial and credible. Because any and every DNA/gene could be used in a microarray,

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regardless of any other characteristic of the DNA/gene, use of the claimed polynucleotide in a microarray would not be a specific utility.

Therefore, a microarray comprising the claimed polynucleotide would not be a specific utility. Applicant has argued that the Office is requiring a utility that is "unique", i.e. not shared by any other compounds or compositions. However, Applicant is required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.).

The Declaration of T. Bedilion (dated 20 October 2003) filed under 37 CFR § 1.132 has been carefully considered, but is not persuasive to overcome the rejections of record. The Declarant worked for Synteni Inc., which was later acquired by Incyte Corporation. T. Bedilion states that customers of the company wanted arrays with more genes. T. Bedilion states

I should note the customers were not asking for addition of probes specific to only those genes for which the biological function of the encoded gene product was known, but were asking for probes specific to any and all expressed genes.

The Declaration of T. Bedilion does not mention the claimed invention, and is not directed to the invention claimed by Applicant. The statements in the Declaration are consistent with the state of the art at the time of the instant invention, which is that microarrays should contain "any and all expressed genes". Therefore, the claimed invention would not have utility based on the

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incorporation of that nucleic acid on a microarray, because this would not constitute a specific utility of the claimed invention because this use would apply to all nucleic acids regardless of the specific properties of the claimed nucleic acid.

The Declaration of T. Bedilion (dated 15 October 2003) filed under 37 CFR § 1.132 has been carefully considered, but is not persuasive to overcome the rejections of record. The Declarant concludes that

persons skilled in the art on December 31, 1997 would have understood the Lal '485 application to disclose the use of the SEQ ID NO:25-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at the time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs.  
(paragraph 6 of Declaration)

In reaching his conclusion, the Declarant cites 8 references, which will be summarized below.

(a) Schena et al. PNAS USA 93 : 10614-10619, 1996. This reference describes the use of cDNA microarrays for "human gene expression monitoring, biological investigation, and gene discovery" (page 10614, column 1, bottom). This reference does not discuss use of the claimed polynucleotide or an array comprising the claimed polynucleotide. The microarrays of the reference contained 1046 human cDNAs of unknown sequence (see abstract). Schena et al. also state

Microarrays of 100,000 cDNA elements would allow expression monitoring of the entire human genome in a single hybridization. This capacity,

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coupled with detailed biochemical analysis of the individual gene products, would greatly speed the functional analysis of the human genome.

(b) Schena et al. Science 270 : 467-470, 1995 is directed to using microarrays in order to quantitate expression of many cDNAs at one time. Schena et al. state "the temporal, developmental, topographical, histological, and physiological patterns in which a gene is expressed provide clues to its biological role." Schena et al. does not teach the claimed invention or a microarray comprising the claimed nucleic acid.

(c) WO 95/35505 is directed to methods and apparatus for forming microarrays of biological samples. This reference does not reference the claimed invention or discuss the significance of any single data point derived from the results of the microarray of the WO document. Pages 29-32 discuss how the microarray would be used, including comparing patterns of expression, comparing unknown DNA to an array with known DNA, screening a patient's DNA against known mutations in a disease gene. In applications of analyzing patterns of gene expression and comparisons made from these patterns, the content of the microarray (i.e. the genes included on the microarray) is not critical. For applications of determining the presence of a pathological condition or presence of a genetic mutation, the knowledge of the genes on the microarray is necessary.

(d) U.S. Patent No. 5,807,522 is directed to methods of forming microarrays. This reference does not reference the claimed invention or discuss

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the significance of any single data point derived from the results of the microarray.

(e) DeRisi et al. *Nat. Genet.* 14(4) : 457-460, 1996 used a cDNA microarray to analyze gene expression patterns in UACC-903 cells, which is a human melanoma cell line. The microarrays contained 1,161 elements, including 870 different cDNAs and controls. Data obtained was relative expression levels in the melanoma cell line compared to a non-tumorigenic derivative to identify genes that were expressed at a greater level in the tumor cell line. Differences in expression between the two cell lines identified "several genes as candidates for determining features of the tumorigenic phenotype of the melanoma cells" (see page 457, column 2, last paragraph). Therefore, DeRisi et al. used the microarray to examine a pattern of expression, which did not rely upon the nature of the genes included in the microarray. Further analysis regarding disease state or identification of genes involved in tumorigenic phenotype required additional analysis and knowledge of the gene itself.

(f) Shalon et al. *Genome Res.* 6(7) : 639-645, 1996 is directed to using microarrays to analyze complex DNA samples. The microarray used contained 1744 elements and was used for quantitative monitoring of gene expression patterns. Again, the specifics of the DNAs included on the microarray do not appear to be critical because the results are looking for a pattern of expression which could be obtained with any collection of DNA molecules. While the pattern would be different depending on which DNA molecules are present in the array, it is the comparison that is important (normal tissue versus disease tissue;

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expression in the presence and absence of a compound; expression pattern in a toxic response compared to expression pattern after administration of un-tested compound). Therefore, Shalon et al. does not support the position that inclusion of the claimed nucleic acid molecule in a microarray provides a specific utility for the claimed nucleic acid molecule itself.

(g) Heller et al. PNAS USA 94 : 2150-2155, 1997 used microarrays to study genes which may be involved in inflammation. Heller et al. used two different types of microarrays; one contained 96 known human genes of probable significance in rheumatoid arthritis and the second contained 1056 human genes from a peripheral blood lymphocyte library. Patterns of expression were obtained from both microarrays. In the case where the genes were known, investigators could make predictions and observations regarding the significance of the particular genes in the disease being studied. In the microarray containing the genes from the tissue library, investigators look for genes that are upregulated (have brighter signal) and study them further which can include sequencing the DNA to determine what gene is represented in order to determine the significance of the upregulation (see page 2154, column 2, paragraph 2). The incorporation of the unknown genes on the microarray did not require any specific properties of the genes, therefore, any genes would have sufficed. This is not a specific utility for the genes since it is a utility that would apply to any gene/DNA. While the microarray can be used to provide new targets for drug development (i.e. genes that are upregulated in disease state compared to healthy tissue), the involvement of any one gene is not known until the

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microarray is examined and after identification of candidate genes, further testing is required to reasonably confirm any involvement in the disease condition. This utility is not substantial because it is not in a currently available form for the skilled artisan and requires further experimentation to reasonably confirm the asserted utility.

(h) Sambrook et al. provides a general understanding of the methods used to quantitate mRNA. Sambrook et al. does not relate to patentability of microarrays or discuss the claimed invention.

The Declaration states in paragraph 8 that "one of ordinary skill in the art would have recognized that the SEQ ID NO:25-encoding polynucleotides could be used in toxicology testing and drug development, irrespective of the biochemical activities of the encoded polypeptide" and that "SEQ ID NO:25-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of that specific polynucleotide in cDNA microarrays". In paragraph 9, Declarant states that the Declaration "focuses on the portions of the application that relate to the use of the SEQ ID NO:25-encoding polynucleotides in gene expression monitoring applications". These statements are noted, however, the issue for the instant application is not whether one could use the claimed polynucleotide in a microarray. To the contrary, the references cited by Declarant demonstrate that microarrays can contain any DNA and use of the microarray does not hinge on the DNA contained in the microarray. The references cited demonstrate that microarrays were known in the art and used in the art for a number of

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applications in which gene expression monitoring is required. However, the references do not establish patentable utility for the claimed polynucleotides based on the inclusion of the claimed polynucleotides in a microarray. As described by the references and Declarant, use of polynucleotides in a microarray is not a specific utility because it is a use that would apply to all polynucleotides regardless of the specific properties of the individual polynucleotides, including the claimed polynucleotides.

Declarant's summary of the cited references appears in paragraphs 11-14. The Examiner summarizes these references above. At paragraph 15, Declarant states that the specification of the instant application would have led a person skilled in the art of developing new drugs for the treatment of cancer and immunological disorders at the time of the invention to "conclude that a cDNA microarray that contained the SEQ ID NO:25-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:25-encoding polynucleotides". This conclusion is noted, but seems to rely on facts that are not part of the record. There is no showing that the claimed polynucleotides are involved in cancer or immunological disorders, therefore, there would be no reason for a person skilled in the art of developing new drugs for treatments in these areas to request the claimed invention for this purpose. While the references cited support the conclusion that those skilled in the art of gene expression monitoring find microarrays containing larger numbers of genes more useful (or robust) than microarrays containing fewer numbers, this does not

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support the conclusion that the claimed polynucleotide was any more desirable than any other polynucleotide. Use of any one polynucleotide in a microarray is not a specific utility because the microarray is a tool that generates a pattern of expression and this pattern does not require any specific properties of the polynucleotides contained within the microarray.

Once a pattern of expression is generated, it can be compared to normal tissue to detect differences in gene expression. Sometimes it is just the pattern that is used to make conclusions regarding disease state, toxic response, etc. For example, a specific toxin may generate a very distinctive pattern. If a compound being tested generates a pattern similar to that of the known toxin, then one may conclude that the compound is also toxic. In another example, cancerous tissue may generate a distinctive pattern in a microarray, and this could be used to compare unknown samples for detection of cancer. Again, the specifics of the genes contained in the microarray are not necessary for generating the expression pattern, therefore, the utility of any one gene (or polynucleotide) in the microarray is not specific.

At pages 12-13 of the Declaration (paragraph 15(e)), Declarant states that the specification teaches that the polynucleotide of SEQ ID NO:102 came from cecal tissue cDNA library and that northern analysis shows expression in cDNA libraries, 50% of which were associated with fetal development/cell proliferation and 25% with immune response. Declarant concludes that persons skilled in the art "would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cancer and

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immunological disorders .. contain any one of the SEQ ID NO:25-encoding polynucleotides as a probe." However, the facts of record do not support this conclusion because the fact that the claimed polynucleotide of SEQ ID NO:102 was expressed in cDNA libraries associated with immune response or fetal development, this in no way, shape or form indicates that the claimed polynucleotides are involved in immune response or fetal development.

Furthermore, there are no facts of record that would support a conclusion that the claimed polynucleotides play any role in cancer. Therefore, there is no motivation for persons skilled in the art conducting gene expression monitoring studies on drugs for treating cancer and immunological disorders to request the claimed polynucleotides in lieu of any other available polynucleotide for use in microarrays for these kinds of studies. This is because the claimed polynucleotides are just another spot in the pattern generated using the microarray and a spot can be generated by any polynucleotide used in the microarray. Because there is no known function or biological activity for the claimed polynucleotides or the proteins encoded thereby, there is no motivation to use this polynucleotide over any other available polynucleotide. Likewise, if the claimed polynucleotide generates a signal in a microarray, apart from being part of the larger pattern of expression of the entire microarray, what is the significance of this signal? Without further research on the claimed polynucleotide itself, what would a person skilled in the art ascertain from altered expression of polynucleotide in a microarray? Away from the context of the entire pattern of the microarray, the expression of a single polynucleotide with unknown

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function/activity/significance provides no useful information to the skilled artisan with respect to treatment of cancer or immunological disorders or drug discovery.

Declarant, at paragraph 16, states that use of the claimed polynucleotide is not limited to use of just the polynucleotide of SEQ ID NO:102 in microarray applications, but also for non-microarray techniques. This statement is noted, but the ability to use the claimed polynucleotide in other hybridization applications does not impart a patentable utility to the claimed invention.

Detection of the claimed polynucleotide in a sample is not useful in a real-world sense to those skilled in the art because the significance of its presence is unknown. The claimed polynucleotide cannot be used to diagnose diseases or disorders because there is no known correlation or nexus between the claimed invention and any disease. The fact that a skilled artisan could use the claimed invention to search for a disease that may be correlated to altered expression of the claimed invention does not meet the requirements of § 101 because the invention does not provide a "specific benefit in currently available form" (further research is required to discover what disease may be correlated with the claimed invention).

Therefore, the Declaration of T. Bedilion (dated 20 October 2003) filed under 37 CFR § 1.132 has been carefully considered, but is not persuasive to overcome the rejections of record. The evidence and opinion provided do not establish a specific, substantial and patentable utility for the claimed invention. Inclusion of the claimed invention in a microarray does not convey a patentable utility to the claimed polynucleotides because use of a polynucleotide in a

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microarray is not a specific utility because it is a use that would apply regardless of the specific properties of the claimed polynucleotides. Any and every polynucleotide can be used in a microarray and the art recognizes that any and every polynucleotide finds use in a microarray, therefore, this use is not specific and does not meet the requirements of § 101.

The Declaration of J. Rockett III filed under 37 CFR § 1.132 has been carefully considered, but is not persuasive to overcome the rejections of record. The Declarant has knowledge of toxicology research and expression profiling techniques. Declarant states at paragraph 4 that “expression profiling, by reporting the expression levels of thousands of genes simultaneously, gives us an opportunity to identify and group toxicants based on similarities in the patterns of gene expression they induce in cells and tissues”. The patterns of gene expression induced by agents of unknown toxicity are compared and judged against the patterns of gene expression induced by known toxins. In paragraph 14 with regard to protein expression profiling, Declarant states “the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required”. In paragraphs 15-17, Declarant makes clear that the information gained from expression profiling is the “pattern” of expression, and it is the “pattern” of expression that is used to make determinations regarding toxicity and the like.

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As indicated above with regard to Bedilion, one of skill in the art would use the microarray to generate a pattern of expression, and therefore, is not necessarily concerned with any individual signal from any individual polynucleotide contained in the array. Therefore, any collection of polynucleotides contained in a microarray would be capable of providing a pattern of expression. Because any polynucleotide could be used in a microarray, this use is not specific and does not meet the requirements of § 101. The specific properties of the claimed polynucleotide are not necessary for its use in a microarray, therefore, this use is not specific.

### ***Response to Applicant's Arguments***

At pages 11-20, Applicant summarizes the references cited in the Declarations and/or submitted as evidence in this response. The Examiner has likewise provided a very brief summary of the documents relied upon in the Declarations. A summary of each and every document does not appear to be necessary. In general, none of the documents indicates the utility of the individual polynucleotides contained in the microarray or the significance on the individual polynucleotides contained in the microarray. The documents indicate that microarrays are used in the art for expression profiling. This point is not disputed. The conclusion of the Board that "the asserted utility of the claimed polynucleotides – as a component of a microarray for monitoring gene expression – does not satisfy the utility requirement of § 101" is the point of contention.

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Applicant asserts that (1) the skilled artisan could use the claimed invention for expression analysis regardless of the biological function of the molecules and (2) uses for the claimed invention are not limited to microarrays. Applicant also asserts that the Declarants indicate that (1) differential screening, (2) subtractive hybridization, (3) differential display, (4) restriction endonuclease facilitated analyses, and (5) EST analysis all use differential expression analysis technologies. However, for the reasons provided above, use of the claimed polynucleotides in expression analysis techniques, such as microarrays, does not provide a specific utility for the claimed invention because this is a use that could be applied to any polynucleotide, regardless of the specific properties of the polynucleotide used. As for use in the methods of (1)-(5), these uses also do not require any specific property be possessed by the polynucleotides being used in the methods (observing patterns generated), therefore, these uses would also not meet the requirements of § 101.

Applicant addresses the Board's concerns regarding "specific utility" beginning at page 22 of the response. Applicant asserts that the claimed polynucleotides are "gene-specific probes" which depend upon "specific properties of the polynucleotides, that is, their nucleic acid sequence". Applicant's arguments have been carefully considered, but are not persuasive. Applicant appears to be mixing the scientific definition of "specific" (i.e. meaning that the probe in the array will only binding to the cognate transcript) with the meaning of "specific" as it applies to the utility requirement of 35 USC § 101. While it is true that the skilled artisan can use microarrays to generate expression

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profiles (i.e. a pattern of spots in a grid), this ability of the skilled artisan to generate data in a microarray does not require the specifics of the polynucleotides contained in the microarray. The microarray will generate a pattern of expression, regardless of the specific polynucleotides employed. The microarray pattern will change depending on the collection of polynucleotides contained within, but since the analyses of data compares the patterns of the microarrays, it is not critical for obtaining useful data. Therefore, even though a skilled artisan would value the inclusion of as many polynucleotides as possible in a microarray in order to increase "the resolving power" of the microarray, this is similar to increasing the number of pixels for a digital picture. The specific properties of the polynucleotides used to increase "the resolving power" is not important, but rather the sheer number of polynucleotides included in the microarray available to hybridize and generate expression data.

At page 23 of the response Applicant states that microarrays have a well-established utility and rejection of Applicant's claim to a microarray comprising the claimed polynucleotides implies "that the addition of Appellants' SIGP-25 polynucleotides to a microarray deprives the microarray of all its utility". Applicant's argument has been carefully considered, but is not found persuasive to overcome the rejections of record. First, the references and declarations provided by Applicant demonstrate that microarrays are used in the art for a number of different purposes. However, the recitation of "microarray" does not convey any specific utility because its use does not depend on the specific properties of the polynucleotides in the microarray. For example, the recitation of

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“microarray” can be compared to a recitation of “pharmaceutical composition”.

Both have known uses in the art, but the specific utility of both depend on context in which they are used and the components found in each. Any microarray that contains polynucleotides can be used to generate a pattern of gene expression.

However, that pattern alone does not provide a “specific benefit in currently available form” without more. The additional information would be comparison of different expression patterns of normal tissue versus diseased tissue or comparison of expression patterns with or without addition of a compound (i.e. testing “toxicity”). Therefore, since a microarray can contain any polynucleotides and be used for any expression monitoring application, it would not have a utility that is considered specific and substantial to satisfy the requirements of §101.

This is not to say that particular microarrays do not have utility; this issue is not before the Examiner. The issue at hand is whether the inclusion of the claimed polynucleotide (found to lack utility by the Examiner and the BPAI) in a microarray now provides a specific and substantial utility for the claimed invention. The answer would have to be no. As the Board iterated, assuming arguendo that a generic microarray – one comprising thousands of uncharacterized or semi-characterized gene fragments – would provide a useful tool, it does not follow that each one of the genes represented in the microarray individually has patentable utility. Although each gene in the microarray contributes to the data generated by the microarray overall, the contribution of a single gene – its data point – is only a tiny contribution to the overall picture.

Looking at this issue from a different point of view, consider a microarray lacking

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the claimed polynucleotide. The skilled artisan would still be able to use the microarray for whatever gene expression monitoring study they want; what additional specific and substantial use does the addition of the claimed polynucleotide add to the microarray? The microarray would be just as useful for generating a pattern of expression regardless of whether Applicant's claimed polynucleotide were included or if a different, uncharacterized polynucleotide were present. "Each claimed invention must be shown to meet § 101's utility requirement in order to be patentable; it must provide a specific benefit in currently available form. Providing a single data point among thousands or millions, even if the thousands or millions of data points collectively are useful, does not meet this standard." (BPAI decision at page 28).

At pages 24-25 of the response Applicant argues that the claimed nucleic acid is 99.2% identical to a polynucleotide encoding human chemokine beta-2 and that the evidence cited by the Board shows a well-established utility for the claimed invention. Applicant's arguments have been fully considered, but are not found persuasive. All that the specification discloses regarding SIGP-25 specifically is that it has 28% sequence identity to a protein identified as "mouse beta chemokine, Exodus-2 (GI 2196924)". No further information is provided regarding the activity or function of either the protein encoded by the claimed polynucleotides or the mouse chemokine with which it has 28% sequence identity. The evidence of record shows that chemokines have widely varying activities *in vivo*. The specification specifically states that "[c]hemokines have been shown to be active in cell activation and migration, angiogenic and

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angiostatic activities, suppression of hematopoiesis, HIV infectivity, and promoting Th-1 (IL-2-, interferon  $\gamma$ -stimulated) cytokine release.” (page 7).

Applicant also cited Rossi which shows in Figure 1 that chemokines can be involved in lymphoid trafficking, wound healing, Th1/Th2 development, angiogenesis/angiostasis, metastasis, cell recruitment, inflammation, or lymphoid organ development. The specification provides no basis for concluding which, if any, of the activities of the various known chemokines is shared by SIGP-25.

Thus, although the evidence supports Applicant's position that some chemokines are involved in immunological disorders, and some chemokines are involved in tumorigenesis and metastasis, there is no evidence that all chemokines are involved in any of these processes, nor that SIGP-25 is involved in any of them, nor that a person of skill in the art would have appreciated that the identification of SIGP-25 as a chemokine, without more, would have suggested any specific and substantial patentable utility.

Applicant refers to human chemokine  $\beta$ -2 and the issuance of U.S. Patent No. 5,981,231 as providing support for the assertion of a well-established utility for the claimed invention. However, each application is examined on its own merits and the Examiner will not comment on the prosecution of any other application. However, it is noted that U.S. Pat. No. 5,981,231 discloses that CK $\beta$ -15 is expressed only in the thymus and that it mediates the differentiation of intrathymic T cell precursors into mature T-lymphocytes as well as directing the homing of the immature lymphocytes precursor to the thymus for proper maturation; this disclosure is absent from the instant specification.

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Applicant cites *Ex parte Skuballa*, 12 USPQ2d 1570 (1989). Applicant states:

as the Board held in a case in which multiple utilities relating to multiple biological effects of prostacyclins were claimed in a single pharmaceutical claim, so long as what is known in the art, coupled with the teaching of the specification, provides "fully adequate guidelines as to intended utilities and how the uses can be effected," such uses can be effected. Even if some experimentation is required to determine optimum conditions for particular uses "in order to achieve a particular biological response, such experimentation is not considered to be undue".

Applicant's summary of the Board decision appears to omit essential information necessary to understand the holding (which is not consistent with Applicant's summary, in the Examiner's opinion). First, the invention at issue was directed to prostacyclin derivatives, which were found patentable.

Therefore, the compounds claimed were tested and found to have a particular biological activity consistent with prostacyclins known in the art. The claims rejected by the Examiner were directed to pharmaceutical compositions, as well as methods of effecting a number of biological activities, such biological activities having been attributed to the known prostacyclins in the art. The Board decided that the claims were enabled and definite because the specification taught "that the novel prostacyclins of the present invention, although more selective with regard to potency, exhibit the properties typical for the prostacyclins of the prior art and may be utilized to achieve similar biological responses". Conventional dosages for the known prostacyclins were set forth in the specification, therefore, "while some experimentation may be required to determine optimum dosages for

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these more potent prostacyclins in order to achieve a particular biological response, such experimentation is not considered undue”.

Utility of the claimed compounds was never an issue in the case before the Board. The specification of the case before the Board established a biological activity for the claimed compounds, which was consistent with the known compounds in the prior art. The instant specification has alleged activities for the claimed invention to be similar to a family of proteins which have diverse biological activities. The biological activities possessed by different proteins in the family of chemokines are not the same or consistent between the members of the protein family (meaning, not every protein has the same activity or same group of activities). The instant specification has not tested the claimed invention for any particular activity. Therefore, the fact pattern of the instant application is not analogous to that of Ex parte Skuballa because the issue before the Board is different (enablement versus utility) and because Skuballa had already established a utility for the compounds being claimed. The experimentation required by Skuballa is routine because the compounds were already known to have particular biological activities and determination of “optimum dosages” has been established to be routine in the art. In the instant application, the experimentation required to use the claimed invention is the actual determination of utility for the claimed invention. The MPEP makes clear that when further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101.

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Until an invention is refined and developed to the point where specific benefit exists in currently available form, there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. At this point in time, specific benefit of the claimed invention has not been identified as it relates to classification of the encoded protein as a chemokine because further experimentation is required to identify what biological activity of the chemokine family is possessed by the claimed invention.

At page 25 of the response, Applicant cites *Brenner v. Manson*, *Brooktree Corp. v. Advanced Micro Devices, Inc.*, *Fuller v. Berger* and *Juicy Whip v. Orange Bang Inc.* Applicant appears to be asserting that because measurement of the level of the expression of the claimed polynucleotide contributes to the pattern of expression in a microarray, even if it is a tiny contribution, such contribution "would assuredly suffice under 35 U.S.C. § 101." However, the use of the claimed invention in this manner is not a specific use because this contribution to the overall pattern (i.e. pixel in the picture of the microarray) could be generated by ANY polynucleotide. The claimed invention does not provide a "specific benefit in currently available form". Without more, the significance of expression of the claimed polynucleotide in a microarray is unknown and the data generated from the claimed polynucleotide alone would not provide any "specific benefit". The specific properties of the claimed invention are not necessary for its use in the microarray when the only information being obtained from its use in the microarray is as part of an overall pattern, which can be generated using any polynucleotide.

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Claim 33 is directed to a microarray "containing at least one polynucleotide of claim 30", wherein the elected invention is the polynucleotide of SEQ ID NO:102. Taking the claimed microarray to its most simple embodiment would equate to the claimed polynucleotide, SEQ ID NO:102, attached to a solid support. What information would be gained by detecting the expression of this polynucleotide in the presence of a toxin or a potential therapeutic agent? While one can measure the expression level of the claimed polynucleotide in the presence and absence of such a compound, there is no meaningful information to be gained because the polynucleotide is uncharacterized and an increase or decrease in expression levels have not been correlated to any disease or function. Any uncharacterized polynucleotide could be measured in this manner, but the data obtained from a single polynucleotide does not generate a "pattern of expression" which is what is used in a microarray for making determinations of drug toxicity, etc. While it is true that researchers use specific polynucleotides in arrays to make conclusions regarding disease state, etc., they are using the characterized polynucleotides (i.e. the molecules that are known to play a specific physiological role in disease or biological function). From the information gained in the microarray from the overall pattern of expression and the data obtained from the known, characterized polynucleotides, researchers then begin to attempt to characterize the unknown molecules that are in the array. But until this further research and experimentation is done, the uncharacterized molecules in the array would not have specific and substantial utility to meet the requirements of § 101 because they do not provide a specific benefit in currently

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available form. Applicant's argument that the claimed polynucleotide has utility because it provides a single data point among thousands or millions in a microarray, even if the thousands or millions of data points collectively are useful, does not meet the standards of § 101 for the reasons provided above.

### ***Art of Record***

It is noted that Applicant refers to U.S. Patent No. 5,981,231. The protein in this patent differs from the encoded protein of the instant application in at least one amino acid position (#23). The nucleic acid molecule of the patent is 99.2% identical to the claimed polynucleotide of SEQ ID NO:102. Because the claims require the polynucleotide to either encode the polypeptide of SEQ ID NO:25 or have the nucleic acid sequence of SEQ ID NO:102 (including vectors, host cells, microarrays, methods of making the protein, etc.) and the protein and polynucleotides of the patent are not identical, the patent is not prior art against the claimed invention. There is no motivation present to make the specific changes which distinguish the molecules of the patent and the instant application, therefore, the claims are not obvious over U.S. Patent No. 5,981,231.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is

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filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**CHRISTINE J. SAOUD**  
**PRIMARY EXAMINER**

*Christine J. Saoud*